REMARKS

The Official Action dated November 19, 2002 and the references cited therein have been carefully reviewed. In view of the amendments presented herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

Status of the prosecution:

Claims 16-29 are pending in this application. The November 19, 2002 Official Action is a first action on the merits.

The declaration has been deemed defective because priority for PCT/US98/04291 was claimed under 35 U.S.C. §119 (a)-(d) rather than 35 U.S.C. §120. The examiner states that a new declaration is required.

Claims 16-29 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to enable one of skill in the art to make and/or use the invention. The examiner cited the following references in support of the rejection: Graves et al. (1997) Diabetes 46:161-168; Verma et al. (1997) Nature 389, 239-242; Anderson et al. (1998) Nature 392: 25-30; Kmeic (1999) American Scientist 87: 240-247; Fox (2000) Nature Biotechnol. 18: 143-144; and Tu et al. (1995) J. Virol. 4607-4618.

Claim 18 was rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness in the recitation of "comprises a a coxsackievirus B genome."

No rejections were issued on the basis of prior art.

Amendments presented in this paper:

The specification was amended to update the priority claim and to correct a typographical error. Claim 18 was amended to correct a typographical error. Claim 26 was amended to incorporate the limitation of claim 27, which was canceled.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached pages are captioned "Version with markings to show changes made."

Applicants assert that the claim amendments submitted herewith overcome each of the rejections issued in the November 19, 2002 Official Action, and that the claims as amended are in condition for allowance.

The requirement for a new declaration is traversed.

The inventors' Declaration as filed erroneously states a priority claim to a U.S. – filed PCT application as being pursuant to 35 U.S.C. §119 instead of 35 U.S.C. §120. Applicants submit, however, that this error does not render the Declaration defective so as to require submission of a new Declaration. The presently pending Declaration contains each and every element required in accordance with 37 C.F.R. §1.63. This application is not associated with any prior foreign applications, therefore no such applications are recited in the Declaration. The recitation of prior United States applications in the Declaration is not required (the priority claim to United States applications is correctly stated in the first line of the specification, pursuant to 35 U.S.C. §120). Since the error noted by the examiner appears in information not required in the Declaration, the Declaration should not be deemed defective for containing an error in that information. Applicants accordingly request that the objection to the Declaration be withdrawn.

The claims are enabled by the specification.

A specification that contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Brana,* 51 F.3d 1560, 34 U.S.P.Q.2d 1436, quoting *In re Marzocchi*, 58 C.C.P.A. 1069, 439 F.2d 220, 223, 169 U.S.P.Q. (BNA) 367, 369 (CCPA 1971). The examiner has cited unpredictability in the art of IDDM treatment and gene therapy, lack of guidance and lack of working examples as reasons to deem the claims not enabled in their present scope by the specification. Applicants disagree with the examiner's assessment.

The present invention covers compositions and methods for treating IDDM utilizing a viral vector comprising a coxsackievirus genome modified to encode an attenuated coxsackievirus, the genome further comprising at least one cloning site for insertion of at least one expressible heterologous nucleic acid encoding a biologically active immunomodulatory protein that induces a shift from a Th1 to a Th2 immune response in the individual. The invention also covers a method of suppressing onset of insulin-dependent diabetes mellitus in an individual, which comprises inoculating the individual as a juvenile or infant with a coxsackie B virus.

The compositions and methods are designed for use *in vivo*, as therapy in humans, and also in non-human animal systems (e.g., NOD mice) as research tools/methods to further elucidate the biochemical and physiological basis for IDDM. These utilities are enabled by the specification. The specification provides two (not zero) working examples of the *in vivo*

utility of the claimed compositions and methods. Both working examples utilize the NOD mouse model of IDDM. This model is the most widely used, understood and accepted models of IDDM in use today, as evidenced by the article of Atkinson and Leiter, Nature Medicine 5: 601-604, 999, attached hereto. As stated in that article (page 601), "today when a candidate autoantigen undergoes evaluation, the effect of a cytokine is tested or a preventative intervention is assessed, NOD mice are often considered 'as good as it gets', short of study in humans . . ." This model has been used for over twenty years for pre-clinical evaluation of a variety of agents (see Table page 602). Example 7 of the specification provides evidence that a coxsackievirus vector of the invention expressing IL-4 protects NOD mice against IDDM. Example 8 provides evidence that treatment of juveniles with a CVB suppresses the onset of IDDM in NOD mice. Furthermore, the demonstration of efficacy set forth in Example 8 (supporting claims 26-29) has been expanded to include nine different CVB strains (See Tracy et al., J. Virol. 76: 12097-12111, 2002, attached hereto), confirming the results set forth in the specification that inoculation of juveniles with coxsackieviruses suppresses the onset of IDDM.

The examiner has stated that the arts of IDDM therapy and gene therapy are unpredictable. However, these general statements of unpredictability would carry little weight in view of the specification's *in vivo* proof of efficacy of the claimed compositions, in one of the best understood and most acceptable animal models of IDDM. To require additional *in vivo* evidence would be to require clinical testing in humans, which is beyond the scope of the enablement requirement of 35 U.S.C. §112, first paragraph. In view of the high acceptability and long use of the NOD mouse model, one of skill the art clearly would be able to extrapolate the *in vivo* pre-clinical results obtained from the NOD mouse model in Examples 7 and 8 for development in other animal systems or for clinical study in humans.

Accordingly, the enablement requirements of 35 U.S.C. §112, first paragraph are fully met, and the rejection of claims 16-29 on this ground should be withdrawn.

Claim 18 as amended is definite.

Claim 18 has been amended to delete the extra "a" from the claim, thereby removing the basis for deeming the claim indefinite. Withdrawal of the 35 U.S.C. §112, second paragraph, rejection of claim 18 is therefore requested.

Conclusion.

In view of the amendments submitted herewith and the foregoing remarks, the presently pending claims are believed to be in condition for allowance. Applicants respectfully request early and favorable reconsideration and withdrawal of the rejections set forth in the November 19, 2002 Official Action, and allowance of this application.

Respectfully submitted,

Date: March 19, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

The first paragraph of the specification was amended as set forth below.

--This application is a continuation-in-part of U.S. Application No. 09/403,672, having a filing date of March 27, 2000, now U.S. Patent No. 6,323,024, which is a national stage patent pursuant to [and claiming priority under] 35 U.S.C. §371 of [to] International Application No. PCT/US98/04291, which itself claims priority under 35 U.S.C. §120 to U.S. Application No. 08/812,742, now U.S. Patent No. 6,071,742, issued June 6, 2000. The entireties of each of the above-listed applications are incorporated by reference herein.—

The paragraph beginning on page 15, line 30 was amended as set forth below.

--Figure 12 shows a diagram of the multivalent CVB vaccine construct. The capsid protein [protien] 1D BC loops from CVB2 (B2) and CVB4 (B4) were inserted into the CVB3/0-derived subclone, pBSPL2.--

In the claims:

Claim 27 was canceled; claims 18 and 26 were amended as set forth below.

18. (Amended) The composition of claim 16, wherein the viral vector comprises a [a] coxsackievirus B genome.

26. (Amended) A method of suppressing onset of insulin-dependent diabetes mellitus in an individual, which comprises inoculating the individual as a juvenile or infant with a coxsackie B virus [coxsackievirus].